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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,691	09/05/2001	Angus George Dalgleish	37945-0018	6462

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	13

DATE MAILED: 08/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,691	DALGLEISH ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *2-10 and 13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group II, claims 1, 11 and 12, cell lines PNT2, LNCaP, and NIH-1542, species induction of a decrease in the rate of rise in the level of serum PSA in prostate cancer patient, in Paper Nos: 10 and 12 is acknowledged. The traversal is on the ground(s) that it is improper to apply a factorial approach to Markush groups, and that such an approach would penalize applicant for using the long-accepted Markush claiming forma. This is not found persuasive because claim 1 is a linking claims, and therefore claims that are dependent on claim 1 have been restricted as groups according to MPEP 804.01, as recited in the Office action of paper No:9.

It is noted that the elected combination of three prostate cell lines PNT2, LnCaP and NIH-1542 constitutes a group, and not species.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1, 11-12 are examined in the instant application, wherein claims 1, 11-12 are examined only to the extent of an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising three prostate cell lines PNT2, LnCaP and NIH-1542, wherein PNT2 is derived from normal prostate tissue, LnCaP and NIH-1542 are derived from prostate cancer tissues.

OBJECTION

Claim 1 is objected to for the use of the language "derived". It is not clear how the cell lines are "derived" from normal tissue.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1, 11-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is drawn to an allogeneic "immunotherpeutic agent for the treatment of prostate cancer", comprising three prostate cell lines from three different sources, of which one, two or three cell lines are derived from normal tissue(s), wherein each said normal tissue(s) is (are) from a source which is non-cancerous prostate, wherein the three cell lines are PNT2, LnCaP and NIH-1542. Claims 11-12 are drawn to a composition comprising said allogeneic immunotherpeutic agent and a vaccine adjuvant.

The specification discloses that after administration of a composition comprising one normal and two cancerous prostate cell lines, prostate cancer patients 110 and 404 have an increase in the level of PSA, whereas patient 303 has a decrease in the level of PSA (p.11 and figure 4). The specification also discloses that an increase in T cell proliferation and antibodies against prostate cell line lysates is observed in treated patients (p.10-11, figure 3).

The specification further discloses that administration of normal melanoma cells to a mouse model of melanoma provides some protection against melanoma (p.12).

One cannot extrapolate the teaching in the specification to the claims, because it is unpredictable that prostate cancer is actually treated by administration of three prostate cell lines PNT2, LnCaP and NIH-1542.

Although the PSA level is decreased in one of the three treated patients, a decrease in PSA level is not necessarily an indication that prostate cancer cell growth is inhibited, in view of the possibility that an increase of antibodies against PSA induced by administered prostate cancer cell lines could bind PSA in circulation and the complex eliminated, resulting in a decrease level of detected PSA.

Moreover, although normal melanoma cells could provide some protection against melanoma in a mouse model of melanoma, one cannot extrapolate this result in melanoma to treatment of prostate cancer, because the type and the degree of antigenic stimulus by melanoma cells relevant to melanoma growth are not necessarily similar to those of prostate cells, and because different diseases have different etiology and different responses to therapeutic agents.

Further, it is well known in the art that characteristics of cell lines are different from cells *in vivo*, and thus it is unpredictable the claimed cell lines still retain necessary antigens of prostate cancer *in vivo* to afford protection against prostate cancer. For example, Berthon, P et al, 1995, Intl J Oncology, 6(2): 333-343, teach that none of prostate epithelial cell lines from normal prostate epithelial tissue exhibit immunoreactivity for cytokeratin 14, shown to be marker of the epithelial basal cells in normal prostate *in situ*, and that features such as production of kallikrein 2 or prostate specific antigen, or prostate acid phosphatase disappear in long term culture of human

prostatic epithelial cells in isolation (p. 337, second column, paragraph under Comparative phenotypic characterization of the immortalized human prostastic epithelial cell lines). Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is

recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that the three claimed cell lines would be effective in treating prostate cancer.

Moreover, it is well known in the art that cancer therapy is highly unpredictable. for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the three claimed cell lines would be effective in treating prostate cancer.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in

progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the three claimed cell lines would be effective in treating prostate cancer.

. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph rejection, claims 1, 11-12 are still under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising three killed prostate cell lines PNT2, NIH 1542-CP3TX and LnCaP, does not reasonably provide enablement for an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising "any" three prostate cell lines from three different sources, of which one, two or three cell lines are derived from normal tissue(s),

wherein each said normal tissue(s) is (are) from a source which is non-cancerous prostate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is drawn to an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising three prostate cell lines from three different sources, of which one, two or three cell lines are derived from normal tissue(s), wherein each said normal tissue(s) is (are) from a source which is non-cancerous prostate. Claims 11-12 are drawn to a composition comprising said allogeneic immunotherpeutic agent and a vaccine adjuvant.

The specification discloses immortalized normal cell lines PNT1A, PNT2 and PZ-HPV-7, derived from the prostate (p.4, paragraph before last).

Claims 1, 11-12 however encompass an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising "any" three prostate cell lines from three different sources, of which one, two or three cell lines are derived from normal tissue(s).

One cannot extrapolate from the teaching in the specification to the claims. It is well known in the art that there is only a handful of prostate cell lines derived from normal tissues, that are established and immortalized (Berthon, P et al, 1995, Intl J oncology, 6(2): 333-343). It is also well known in the art that each cell line has unique characteristics and properties. Thus since the characterisitics and properties of the claimed any three cell lines are not disclosed, wherein said characterisitics and

properties are not predictable, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection, claims 1, 11-12 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising three "killed" prostate cell lines PNT2, NIH 1542-CP3TX and LnCaP, does not reasonably provide enablement for an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising three prostate cell lines from three different sources, of which one, two or three cell lines are derived from normal tissue(s), wherein each said normal tissue(s) is (are) from a source which is non-cancerous prostate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is drawn to an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising three prostate cell lines from three different sources, of which one, two or three cell lines are derived from normal tissue(s), wherein each said normal tissue(s) is (are) from a source which is non-cancerous prostate, wherein the three cell lines are PNT2, LnCaP and NIH-1542. Claims 11-12 are drawn to a composition comprising said allogeneic immunotherpeutic agent and a vaccine adjuvant.

Claims 1, 11-12 encompass an allogeneic immunotherpeutic agent for the treatment of prostate cancer, comprising three prostate cell lines, two of which are prostate cancer cell lines LnCaP and NIH-1542 that are "alive".

It is not clear how prostate cancer could be treated with prostate cancer cell lines LnCaP and NIH-1542 that are alive, because that the prostate cancer cell lines would grow and form cancer when injected into a patient. Wu TT et al, 1998, Intl J cancer, 77(6): 887-94 teach that LNCaP prostate cancer cell line has osseous metastatic potential *in vivo*. Triest JA et al, 1998, Clinical Cancer Res, 4(8): 2009-14, teach that serial injection PC-3/IF prostate cancer cell line into the prostate produce new prostate cell lines that are tumorigenic and metastasize to lymph nodes.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

July 25, 2003